ANSES Opinion
Request No. 2013-SA-0240

The Director General

Maisons-Alfort, 3 May 2017

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

Endocrine and metabolic risks related to the intake during pregnancy of vitamin D and iodine through food supplements involved in cases of nutrivigilance

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are published on its website.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 3 May 2017 shall prevail.

On 17 December 2013, ANSES issued an internal request in order to assess the risks related to the intake during pregnancy of vitamins and minerals found in food supplements for pregnant women involved in cases of nutrivigilance. The title of the request was modified on 16 August 2016 in order to clarify the scope of the expert appraisal: "endocrine and metabolic risks related to the intake during pregnancy of vitamin D and iodine through food supplements involved in cases of nutrivigilance".

1. BACKGROUND AND PURPOSE OF THE REQUEST

Background

Between the establishment of the French national nutrivigilance scheme in 2009 and 1 January 2016, 44 reports of adverse effects likely to be related to the consumption during pregnancy of food supplements for pregnant women were brought to the knowledge of ANSES.

Eighteen of these reports were subject to a causality analysis undertaken using the method developed by ANSES (2011); the others were deemed non-admissible due to a lack of information or a lack of adverse effects. The adverse effects reported were primarily endocrinological or metabolic (neonatal hypercalcaemia and hypothyroidism), gastroenterological and obstetrical, with in particular two pregnancies terminated on medical grounds. The Working Group on Nutrivigilance determined intrinsic causality as "likely" for two of these cases, "possible" for eleven of these cases, and "unlikely" for five of these cases.

The severity of the effects affecting vulnerable populations (pregnant women and newborns) and the occasionally high causality led ANSES to issue an internal request in order to assess the risks associated with the intake of vitamins and minerals during pregnancy.

In this Opinion, food supplements intended for pregnant women are referred to as “pregnancy” food supplements.

■ Purpose of the request

ANSES issued an internal request in order to assess the risks related to the intake during pregnancy of vitamins and minerals found in food supplements for pregnant women involved in cases reported under the nutrivigilance scheme. In light of the described adverse effects and their recurrence and causality, ANSES chose to focus its study on endocrine and metabolic effects reported under the nutrivigilance scheme associated with the consumption of food supplements containing vitamin D or iodine.

2. ORGANISATION OF THE EXPERT APPRAISAL

This expert appraisal was carried out in accordance with the French standard NF X 50-110 "Quality in Expertise – General Requirements of Competence for Expert Appraisals (May 2003)”.

The issues being appraised fall within the scope of the Expert Committee (CES) on Human Nutrition. ANSES entrusted the expert appraisal to external rapporteurs and the Working Group (WG) on Nutrivigilance. The methodological and scientific aspects of the work were presented to the CES on 13 October 2016. They were adopted by the CES at its meeting on 3 November 2016.

An external expert was interviewed and internal scientific and technical support was provided by the Food Consumption Observatory Unit (Technical memorandum OCA/PP/2014-071) and the Methodology and Studies Unit (Technical memorandum UME/PP/2016-008). This information appears in the WG's expert appraisal report.

Poison control and toxicovigilance centres, the French National Agency for Medicines and Health Products Safety (ANSM) and professional associations representing industries producing “pregnancy” food supplements were requested to provide any reports they had received. The reports provided were included in the Nutrivigilance database and taken into account in this request.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts’ declarations of interests are published on the ANSES website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE CES AND WG

The discussion and conclusions presented below summarise the collective expert appraisal report of the WG on Nutrivigilance and the review undertaken by the CES on Human Nutrition.

■ Neonatal hypercalcaemia and vitamin D

Vitamin D is a fat-soluble vitamin found in food in two forms: vitamin D2 (ergocalciferol), produced by plants, and vitamin D3 (cholecalciferol), of animal origin. These two forms have equivalent biological activity in humans, in which vitamin D is also endogenously synthesised by the deep cells of the epidermis under the direct action of ultraviolet radiation. Dietary vitamins D2 and D3 are

metabolised by the liver into calcidiol [25(OH)D], which is the storage form, and then in the kidneys into calcitriol [1,25$(OH)_2$D], which is the biologically active form of vitamin D (AFSSA, 2001; Mallet, 2014).

- Aetiologies of neonatal hypercalcaemia related to the intake of vitamin D

Some malignant tumours, granulomatosis and Williams-Beuren syndrome can cause hypercalcaemia irrespective of vitamin D intake.
Considering the levels of vitamin D supplied by "pregnancy" food supplements, their consumption alone is not likely to cause hypercalcaemia in mothers or healthy foetuses. However, hypercalcaemia can be observed in cases of hypersensitivity to vitamin D due to a genetic mutation affecting *cyp24A1*, the gene encoding for 24-hydroxylase, an enzyme that inactivates vitamin D. A case of neonatal hypercalcaemia related to vitamin D hypersensitivity (homozygous mutation) was described in particular by Malandain *et al.* (2015). This hypercalcaemia is characterised in particular by low concentrations of PTH (parathyroid hormone) and high concentrations of 1,25$(OH)_2$D. In the event of a homozygous mutation (one in 250,000 people), hypercalcaemia can be observed regardless of the ingested amount of vitamin D. Cases of heterozygous mutations are not as well documented and their prevalence is not defined. A heterozygous child can have *in utero* hypercalcaemia if the (homozygous) mother is hypercalcaemic. Whether or not the child is given vitamin D supplementation at birth, his/her calcium level returns to normal within a few days (Colussi *et al.,* 2014; Dauber *et al.,* 2012; Molin *et al.,* 2015; Schlingmann *et al.,* 2011).

- Dietary intakes and tolerable upper intake level

The food supplements for pregnant women involved in the cases of nutrivigilance supplied between 5 and 10 µg of vitamin D per day, at the doses recommended by the manufacturer.

The Institute of Medicine (IOM) defined a Population reference Intake (PRI) of 600 IU/day (15 µg/day) of vitamin D and an Average Requirement (AR) of 400 IU/day (10 µg/day) of vitamin D for pregnant women (IOM, 2011). As part of updating the dietary reference values of the French National Health & Nutrition Programme (PNNS), ANSES endorsed the values proposed by the IOM for the adult population. ANSES has not yet made a decision regarding food-based dietary guidelines for pregnant women; the values proposed by the IOM for this population have been used by default in this Opinion.

Although the estimated nutritional requirements are inaccurate and too high, it is estimated that almost all women in France have insufficient intakes. Additional intake of 5 to 10 µg/day is likely to significantly improve the situation.

Considering the theoretical administration of 10 µg/day of vitamin D in addition to dietary intake, there is no risk of exceeding the tolerable upper intake level (UL), as set by the IOM (2011) and EFSA (2012) at 100 µg/day.

- Clinical data

Only one case of moderate neonatal hypercalcaemia following maternal administration of vitamin D all throughout pregnancy (17 to 36 µg/day, i.e. 680 to 1440 IU/day) has been reported (Marx *et al.,* 1980).
The available studies do not show any effects or show a protective effect of vitamin D on risks of pre-eclampsia, anomalies in anthropometric parameters, poor pregnancy outcome, maternal or neonatal infection, impaired bone mineralisation (in the mother or child) or gestational diabetes (Baker *et al.,* 2010; Bodnar *et al.*, 2007; De-Regil *et al.,* 2016; Fares *et al.,* 2014; Farrant *et al.,* 2009; Gale *et al.,* 2008; Hollis *et al.,* 2011; Lagiou *et al.,* 2005; Morley *et al.,* 2006; Powe *et al.,* 2010; Reif *et al.,* 1988; Robinson *et al.,* 2010; Scholl and Chen, 2009; Shand *et al.,* 2010;

Soheilykhah *et al.,* 2010; Wagner *et al.,* 2013a; Wagner *et al.,* 2013b; Watson and McDonald, 2010; Yorifuji *et al.,* 2008).

An increase in the risk of asthma and eczema during childhood was associated with a maternal calcidiol status above 75 nmol/L (Gale *et al.,* 2008). However, other studies did not show any effects or showed a protective effect of vitamin D on the risks of asthma and wheezing in children (Camargo *et al.,* 2011; Camargo Jr *et al.,* 2007; Chawes *et al.,* 2016; Devereux *et al.,* 2007; Litonjua *et al.,* 2016).

- Cases of neonatal hypercalcaemia in nutrivigilance

For the five adequately documented cases of neonatal hypercalcaemia admissible as part of the nutrivigilance scheme, the causal link between hypercalcaemia and the food supplement was found to be unlikely or possible.
The combination of hypercalcaemia, low PTH and high $1,25(OH)_2D$ in addition to ruled-out aetiologies left two possible aetiologies: a vitamin D hypersensitivity syndrome or a malignant tumour secreting PTH-rP (PTH-related protein). In all these cases, the cessation of vitamin D and suitable treatment resulted in the gradual normalisation of calcium levels with no nephrocalcinosis.
As the other aetiologies were ruled out, PTH-rP testing and testing for a *cyp24A1* gene mutation may have confirmed the cause of these observed cases of hypercalcaemia.

Congenital hypothyroidism and iodine

Iodine is essential to the synthesis of thyroid hormones such as triiodothyronine (T3) and tetraiodothyronine or thyroxine (T4). The endocrine secretion of these hormones regulates major physiological functions, from foetal development.

- Aetiologies of congenital hypothyroidism

Congenital hypothyroidism may be permanent or transient.

  - Permanent congenital hypothyroidism

In the two cases of congenital hypothyroidism reported under the nutrivigilance scheme, thyroid-stimulating hormone (TSH) was high, which with permanent hypothyroidism, suggests a peripheral (or primary) cause. Primary hypothyroidism is mainly caused by thyroid dysgenesis (85% of cases) or a genetic defect in hormone synthesis (Rastogi and LaFranchi, 2010).

  - Transient congenital hypothyroidism

Transient congenital hypothyroidism can be related to a maternal deficiency in dietary iodine (Gaudino *et al.,* 2005; Zimmermann, 2011) or to excessive maternal iodine (intake through food or through oral or dermal medicated treatment) (Bartalena *et al.,* 2001; Chanoine *et al.,* 1988; Connelly *et al.,* 2012; Emder and Jack, 2011; Lomenick *et al.,* 2004; Nishiyama *et al.,* 2004; Pennington, 1990). Other aetiologies include maternal treatment with synthetic anti-thyroid drugs (Diav-Citrin and Ornoy, 2002; Rosenfeld *et al.,* 2009); placental transfer of maternal TSH receptor-blocking antibodies in maternal Basedow disease (Brown *et al.,* 1993; Pacaud *et al.,* 1995); and a heterozygous mutation in the gene involved in generating hydrogen peroxide (THOX2) (Moreno *et al.,* 2002; Zamproni *et al*., 2008).
Subclinical transient neonatal hypothyroidism can also be induced by the repeated application of iodine-containing antiseptics in premature infants (Linder *et al.,* 1997).

- Dietary intakes and tolerable upper intake level

The food supplements for pregnant women involved in the cases of nutrivigilance supplied between 120 and 150 µg of iodine per day, at the doses recommended by the manufacturer.

EFSA (2014) defined an Adequate Intake (AI) of 200 µg/day for pregnant women. As part of updating the food-based dietary guidelines of the PNNS, ANSES endorsed the dietary reference values proposed by EFSA for the adult population. ANSES has not yet made a decision regarding food-based dietary guidelines for pregnant women; the values proposed by EFSA for this population have been used by default in this Opinion. Since average iodine intakes are below the AI, it is not possible to know if or to what extent requirements are met by food alone.

For adolescent females (15-17 years), consuming 150 µg/day of iodine in addition to everyday dietary intake does not cause any risk of exceeding the tolerable upper intake levels (ULs) set by the IOM (2001) at 900 µg/day and by EFSA (2006) at 500 µg/day. For women aged 18 to 50 years, this risk is non-existent for the UL of the IOM (1100 µg/day) and close to zero (0.12%) for the UL of EFSA (600 µg/day).

- Clinical data

An adequate iodine status helps prevent prematurity and perinatal mortality. It is necessary for the neurological development and normal behaviour of newborns (Bath *et al.,* 2013; Bougma *et al.,* 2013; Chaouki and Benmiloudl, 1994; Ghassabian *et al.,* 2014; Hynes *et al.,* 2013; O'Donnell *et al.,* 2002; Pharoah *et al.,* 1976; Qian *et al.,* 2005; Santiago *et al.,* 2013; Zimmermann, 2011).

However, excess iodine intake (oral or transdermal) during pregnancy increases the risk of hypothyroidism, hyperthyroidism and goitre in newborns (Bartalena *et al.*, 2001; Caron *et al.,* 2006; Connelly *et al.,* 2012; Glinoer, 1997; Nishiyama *et al.,* 2004; Pennington, 1990; Sang *et al.,* 2012; Trumpff *et al.,* 2013).

- Cases of congenital hypothyroidism in nutrivigilance

For the two adequately documented cases of congenital hypothyroidism admissible as part of the nutrivigilance scheme, the causal link between hypothyroidism and the food supplement was possible. However, based on the available data, it was not possible to formally ascribe the hypothyroidism to a particular vector, in particular when the food supplement was not the only source of iodine.

Recommendations of the CES and the WG

For the five adequately documented cases of hypercalcaemia recorded under the nutrivigilance scheme, there were two possible aetiologies: a vitamin D hypersensitivity syndrome or a malignant tumour. Testing for a *cyp24A1* gene mutation and PTH-rP testing could have confirmed the cause of these observed cases of hypercalcaemia. It is possible that consumption of the food supplement revealed vitamin D hypersensitivity. That said, except in one case, the food supplement was not the sole source of vitamin D.
Similarly, for the case of hypothyroidism related to iodine excess, the food supplement was not the sole source of iodine. Application of an iodine-containing antiseptic during childbirth may have increased the risk of iodine excess for the mother and child.

Based on these observations, the Working Group on Nutrivigilance and the Expert Committee on Human Nutrition are issuing the following recommendations:

- Vitamin D hypersensitivity, with an estimated incidence of 1/250,000 for the most clinically significant homozygous mutation, is not currently subject to systematic screening.
    - Even subclinical maternal hypercalcaemia can in particular be a sign of vitamin D hypersensitivity. Healthcare professionals should pay attention to this during pregnancy. The measurement of calcium levels could be included in the blood tests performed during pregnancy.
    - In the event of hypercalcaemia in pregnant women, its cause should be determined and the relevance of maternal vitamin D supplementation should be discussed.
    - When there is neonatal hypercalcaemia with no identified aetiology, the child should be tested for a *cyp24A1* gene mutation.
        - In the event of a confirmed homozygous mutation, the child should no longer receive vitamin D and sun exposure should be limited. The parents' attention should be drawn to the risk of vitamin D hypersensitivity for their other children.
        - In the event of a heterozygous mutation, in the absence of scientific data, children should be closely monitored in order to tailor doses of vitamin D to each case. Both parents should also be tested for the mutation in view of a future pregnancy.
- Simultaneous exposure to multiple sources of iodine (from medication or food supplements) should be avoided during pregnancy since it can increase the risk of neonatal hypothyroidism.
- Pregnant women are advised to inform their doctor (general practitioner or obstetrician) or midwife of the use of any products (medication or food supplements), whether taken with or without a prescription. Pharmacists should also provide cautionary advice before dispensing these products.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety adopts the recommendations of the Working Group on Nutrivigilance and the Expert Committee on Human Nutrition.

First of all, ANSES would like to remind pregnant women not to use food supplements without the opinion of a healthcare professional and advises them to inform their doctor, pharmacist or midwife of the use of all products (medication or food supplements) taken with or without a prescription.

The occurrence of sometimes severe adverse effects affecting vulnerable populations (pregnant women and newborns) led ANSES to assess the risks relating to the intake during pregnancy of vitamin D and iodine through food supplements intended for pregnant women and to issue the following recommendations.

Due to the consequences of hypercalcaemia with vitamin D hypersensitivity on the health of newborns, it is necessary to take suitable preventive measures. In the event that hypercalcaemia is

confirmed, the appropriate tests should be made to determine its origin and the relevance of vitamin D supplementation for pregnant women should be reconsidered.

For newborns with unexplained hypercalcaemia, the child should be tested for a *cyp24A1* gene mutation and suitable measures should be taken.

Regarding iodine intakes, simultaneous exposure to multiple sources of iodine (from medication or food supplements) increases the risk of thyroid disorders in newborns and should therefore be avoided during pregnancy.

Besides the cases of vitamin D and iodine which have specifically been reported to the nutrivigilance scheme, the Agency warns against the multiplication of sources of vitamins and minerals, in the absence of biologically established requirements, which can in some cases result in the upper intake levels being exceeded.

In this context, the Agency would like to draw the attention of healthcare professionals to the importance of not combining sources of vitamins and minerals unless there is regular biological monitoring. It also stresses the importance of informing its nutrivigilance scheme of any adverse effects brought to their knowledge that are likely to be related to the consumption of food supplements.

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KEYWORDS

Effets indésirables, nutrivigilance, compléments alimentaires, hypercalcémie, hypothyroïdie, grossesse, vitamine D, iode.

Adverse effects, side effects, nutrivigilance, dietary supplements, food supplements hypercalcaemia, hypothyroidism, pregnancy, vitamin D, iodine.